Supplementary Data

Targeted Recruitment Using Cerebrospinal Fluid Biomarkers: Implications for Alzheimer’s Disease Therapeutic Trials

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For a two-sample comparison of means, the required sample size is proportional to:

$$\frac{\text{Var}(X_1) + \text{Var}(X_0)}{\Delta^2}$$

where \(\text{Var}(X_1)\) and \(\text{Var}(X_0)\) denote the variance of the outcome measure in the treated and untreated groups respectively, and \(\Delta\) is the difference in mean outcome between treatment groups. Let \(X_{low}\), \(X_{high}\), and \(X_{all}\) denote the outcome in low-Aβ level subjects, high-Aβ level subjects, and all MCI subjects respectively. Further, let \(\Delta_{low}\) and \(\Delta_{all}\) denote the assumed treatment effects (difference in means) in a trial recruiting only low Aβ-MCIs and all MCIs respectively.

We now derive the ratio of required sample sizes for a low-Aβ targeted trial to the sample size for an all MCI trial, according to three alternative assumptions regarding the effect of a putative treatment:

a) if treatment reduces the mean outcome proportionately by 100k% in the low-Aβ and by 100k% in the high-Aβ, i.e., \(\Delta_{low} = k\bar{X}_{low}\) and \(\Delta_{all} = k\bar{X}_{all}\), the ratio is:

$$\frac{\text{Var}(X_{low}) + \text{Var}(X_{high})}{\text{Var}(X_{all})}$$

b) if treatment reduces mean outcome by an amount \(k\bar{X}_{low}\), irrespective of whether Aβ is high or low, i.e., \(\Delta_{low} = k\bar{X}_{low}\) and \(\Delta_{all} = k\bar{X}_{all}\), the ratio is:

$$\frac{\text{Var}(X_{low}) + \text{Var}(X_{high})}{\text{Var}(X_{all})}$$

c) if treatment benefits low-Aβ subjects only (by reducing mean outcome by \(k\bar{X}_{low}\)) but not high-Aβ subjects, i.e., \(\Delta_{low} = k\bar{X}_{low}\) and \(\Delta_{all} = pk\bar{X}_{low}\), where \(p\) denotes the proportion of low-Aβ subjects, the ratio is:

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2Performed statistical analysis.

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This ratio is always less than \( p \), but unlike in scenarios a) and b), the ratio depends on \( k \). However, for small \( k \) (i.e., small treatment effects) it is approximately equal to:

\[
\frac{\text{Var}(X_{\text{all}}) + p\text{Var}(X_{\text{low}})}{\text{Var}(X_{\text{all}}) + p\text{Var}(X_{\text{low}}) + (1-p)\text{Var}(X_{\text{high}}) + p(1-p)\bar{X}_{\text{low}}^2} = p^2 \frac{\text{Var}(X_{\text{all}})}{\text{Var}(X_{\text{all}})}
\]

and hence again is independent of \( k \).